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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Barberich et al.

Application No.: 09/527,844 Art Unit: 1617

Filed: March 17, 2000 Examiner: S. Sharareh

For: METHODS FOR THE TREATMENT OF NEUROLEPTIC AND RELATED DISORDERS USING ZIPRASIDONE METABOLITES

Attorney Docket No.: 4821-334 (JD 208423-999333)

COMMUNICATION CONCERNING REPLY BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants wish to thank the Examiner for the courtesy he provided to Hoon Choi, an attorney for Appellants, during the phone conversation of September 1, 2004. This communication is submitted further to that conversation.

Appellants' Reply Brief, which was due August 30, 2004, was submitted August 31, 2004, one day after the non-statutory due date. Due to a docketing error, Appellants were unaware that the final and non-extendable due date for submission of their Reply Brief was August 30, 2004. Upon discovering that the due date has passed on August 31, 2004, Appellants submitted their Reply Brief, together with a Petition for Extension of Time and a Request for Oral Hearing.

According to Manual of Patent Examining Procedure § 710.02 (d), the Examiner has the discretion to consider a paper filed one or two days after the non-statutory due date. As can be seen from the enclosed courtesy copy of the Reply Brief, it does not provide any new evidence, nor does it raise any new issues. Therefore, Appellants respectfully request that their Reply Brief submitted August 31, 2004, be entered into the record and considered by the Examiner.

No fee is believed to be due for the submission of this paper. If any fees are required for the submission of this paper or the Reply Brief, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully Submitted,

Date: September 1, 2004

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Enclosure

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: BARBERICH *et al.*

Application No: 09/527,844 | Group Art Unit: 1617

Filed: March 17, 2000 | Examiner: S. Sharareh

For: METHODS FOR THE TREATMENT OF NEUROLEPTIC AND RELATED DISORDERS USING ZIPRASIDONE METABOLITES | Attorney Docket No.: 4821-334

REPLY BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
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Alexandria, VA 22313-1450

Sir:

Pursuant to the provisions of 37 C.F.R. §§ 1.193(b), Appellants submit herewith a Reply Brief in response to the Examiner's Answer ("the Answer") mailed June 30, 2004.

I. Response to the Examiner's Arguments

A. Claims 1-4 and 6-9 Are Not Anticipated by Davis

In the Answer, the Examiner maintains the rejection of claims 1-4 and 6-9 as allegedly anticipated by the abstract of Davis *et al.*, *CNS Drugs*, 8(2): 153-159 (1997) ("Davis"). In response to Appellants' argument that the Examiner's construction of the term "administration" is incorrect and directly contrary to the well-accepted meaning of the term, the Examiner: 1) repeats that the administration of a ziprasidone metabolite is inherent in the administration of ziprasidone itself; 2) characterizes the claims as "product-by-process" claims, and alleges that such product-by-process claims are not patentable in this case; and 3) alleges that *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373 (Fed. Cir. 2003) is not applicable in this case, based on his own interpretation of *Schering*. Appellants submit that none of these allegations are founded on any legal or scientific principles.

1. The Examiner Provides No Support for the Allegation that the Administration of Ziprasidone Inherently Anticipates the Administration of a Ziprasidone Metabolite

In the Answer, the Examiner concludes, without any basis, that the rejection of claims 1-4 and 6-9 should stand rejected "in view of the all facts presented" because "Appellant[s] has [sic] not provided any showing" that the administration of ziprasidone does not inherently anticipate the administration of a ziprasidone metabolite. Answer, page 6. However, as Appellants explained both during the prosecution and in their Brief on Appeal, the administration of a ziprasidone metabolite according to the claimed invention presupposes that such a metabolite exists outside of the patient's body. Brief on Appeal, page 10. Appellants also previously explained that the administration of ziprasidone itself cannot result in the same *in vivo* activity as the administration of a ziprasidone metabolite. Appellants' Response dated April 4, 2003, page 5. Without addressing any of these issues, the Examiner merely alleges that Appellants have not provided any showing that the claims are not anticipated by Davis. Such an unfounded allegation clearly cannot form a basis for rejecting these claims. *See In re Sang-Su Lee*, 277 F.3d 1338, 1343-4 (Fed. Cir. 2002).

The Examiner further alleges that the claims are anticipated because "the patentability is assessed based on the entire claim which questions whether ziprasidone metabolites can be used for treating or prophylaxis of a disorder ameliorated by the inhibition of serotonin uptake at 5-HT2 receptors." *Id.* However, it is well-settled that the patentability of claims, insofar as it relates to 35 U.S.C. § 102, is assessed by determining whether "each and every element as set forth in the claim is found ... in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) (emphasis added). Despite this well-settled legal principle, the Examiner arbitrarily characterizes the claimed invention, based on what he thinks the claims recite "as-a-whole," and alleges that the claims are anticipated.

However, even if the Examiner's characterization of the claimed invention were correct, the Examiner provides nothing to support his position that the claims are anticipated. All that is provided is a repeated allegation that because Davis discloses the administration of ziprasidone itself, and ziprasidone converts to its

metabolites *in vivo*, "Davis discloses administration of metabolites *in vivo* for the same purpose as those instantly claimed." Answer, page 7 (emphasis added). Not only does this mere allegation fail to dispute the evidence and arguments presented by Appellants, the allegation begs the question, *i.e.*, whether the *in vivo* conversion of ziprasidone would constitute the administration of a ziprasidone metabolite as recited by the pending claims. As Appellants previously submitted, it does not. *See* Brief on Appeal, pages 10-12.

In sum, Appellants submit that the Examiner has not provided any evidence that Davis discloses each and every limitation of claims 1-4 and 6-9, and respectfully request that the Board overturn the Examiner's rejection under 35 U.S.C. § 102.

2. The Examiner's Characterization of the Claims as "Product-by-Process" is Improper and Irrelevant

In the Answer, the Examiner alleges that Appellants "constructively present a product-by-process type argument," and alleges that "the fact that [a] ziprasidone metabolite might have been prepared *ex vivo* is not determinative to the patentability [of the claims] because the product employed in a method claims [sic] may not be limited to the manipulations of the steps creating the product." Answer, page 8 (emphasis added). For support, the Examiner cites *In re Thorpe*, 227 U.S.P.Q. 964 (CFAC 1985), and alleges that the claims are unpatentable since "the patentability of a product does not depend on its method of production." *Id.* These allegations completely miss the mark.[1]

The reason why Appellants emphasized the existence of a ziprasidone metabolite outside a patient's body is to explain how the term "administration" would distinguish the claimed invention from that disclosed by Davis. Appellants are not

[1] *Thorpe* does not provide any support whatsoever for the proposition that "the product employed in a method claim may not be limited to the manipulations of the steps creating the product." Answer, page 8. (emphasis added). Indeed, *Thorpe* does not even concern a product employed in a method claim. All *Thorpe* held was that the patentability of a product, using a process recited by the claims, does not depend on its method of production. *Thorpe*, 227 U.S.P.Q. at 966. However, no product claims are present in this application. Indeed, Appellants are not aware of any legal precedent that provides support for the Examiner's statement that the product employed in a method claim may not be limited to the manipulations of the steps creating the product. Such a conclusory and arbitrary statement, without any support in legal precedent, certainly cannot form a basis for rejecting the pending claims.

asserting that the ziprasidone metabolites themselves are patentable because it was made outside the patient's body. Despite this fact, the Examiner mistakenly characterizes the pending claims as "product-by-process" claims, and makes arguments based on that mistaken characterization that are irrelevant to the patentability of the pending claims or any arguments made by Appellants.

3. The Examiner Misunderstands *Schering*

In response to Appellants' argument that *Schering* clearly indicates that a method of administering a metabolite is not anticipated by prior disclosure of the parent compound, the Examiner, while not disputing the truth of such a statement, alleges that *Schering* is not applicable in this case. In particular, the Examiner alleges that the facts of *Schering* are distinguishable because "[t]he statement relied on [by Appellants] by the *Schering* Court is in reference as to such legal precedents wherein parties of interest met their burden of proof by a declaration of unexpected results or drafted such claims to clearly contain a subject matter patentable over the prior art." Answer, page 9. Even if it were true[2], this allegation completely misses the point.

It is well-settled that the determination of "unexpected results" is irrelevant to the assessment of anticipation. *See, e.g., In re Deuel*, 51 F.3d 1552, 1557 (Fed. Cir. 1995). Instead, it is only relevant to the assessment of obviousness, where a *prima facie* case of obviousness is established. *See* MPEP § 2144.05(III). Despite this fact, the Examiner alleges that claims 1-4 and 6-9 are anticipated because Appellants allegedly did not provide any unexpected results. Because the rejection is based on a misunderstanding of the law, it cannot be maintained.

[2] Appellants fail to see how the Examiner reached the conclusion that "[t]he statement relied on by the *Schering* Court is in reference as to such legal precedents wherein parties of interest met their burden of proof by a declaration of unexpected results or drafted such claims to clearly contain a subject matter patentable over the prior art." *Id.* While the *Schering* Court refers to *Katz*, it specifically refers to the portion of *Katz* wherein it is stated that "a naturally occurring strawberry constituent compound does not anticipate claims to the substantially pure compound." *See Schering*, 339 F.3d at 1381 (emphasis added). Despite this express holding in *Katz*, the Examiner alleges that *Schering* and *Katz* are not applicable because the showing of unexpected results were made in these cases.

B. Claims 1-15 and 50-53 Are Not Obvious

Despite Appellants' argument that the combination of Davis, U.S. Patent No. 4,831,031 to Lowe *et al.* ("Lowe"), and U.S. Patent No. 5,312,925 to Allen *et al.* ("Allen"), does not disclose the administration of a ziprasidone metabolite, and Prakash *et al.*, *Drug Metabolism and Disposition*, 25(7): 863-872 (1997) ("Prakash") does not cure the deficiency, the Examiner maintains the rejection of claims 1-15 and 50-53. In particular, the Examiner alleges that "one cannot show nonobviousness by attacking references individually." Answer, page 10 (emphasis added). Even assuming, arguendo, this were true, Appellants did not individually attack the references. Instead, Appellants argued that the combination of the cited references fails to disclose the claimed invention. *See* Brief on Appeal, page 16.

The Examiner further maintains that "all elements of the instant claims are described" in the cited references because: 1) Davis discloses the administration of ziprasidone for the treatment of neuroleptic disorders; 2) Allen and Lowe teach the synthesis of salts of ziprasidone; and 3) Prakash teaches sulfone and sulfoxide metabolites possess agonistic affinities for 5-HT_2 and D_2 receptors. Answer, pages 10-11. But this combination does not disclose the administration of a ziprasidone metabolite. For this reason alone, the rejection of the claims should be overturned.

Stating that "obviousness does not require absolute predictability of success," the Examiner goes on to allege that "[t]here is always at least a possibility of unexpected results that would ... provide an objective basis for showing that invention, although apparently obvious, was in law nonobvious." Answer, page 11. Not only is this statement unfounded, the Examiner's analysis is based on a misunderstanding of legal principles governing obviousness.[3]

To provide support for this statement, the Examiner cites *In re Merck & Co., Inc.*, 800 F.2d 1090 (Fed. Cir. 1986) and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452 (Fed. Cir. 1984). Neither of these cases support the Examiner's statement. Accordingly, Appellants submit that the Examiner's statement is arbitrary and without any support in legal precedent.

The Examiner's analysis further confuses the distinct principles "unexpected results" and "reasonable expectation of success." Again, "unexpected

[3] It is also unclear how this proposition relates to an assessment of obviousness of the pending claims.

results" are required only where a *prima facie* case of obviousness is established by the Patent Office. *See, e.g., In re Deuel*, 51 F.3d 1552, 1557 (Fed. Cir. 1995). Yet, the Examiner, in alleging that a reasonable expectation of successfully obtaining the claimed invention existed, essentially provides that such an expectation was present because no unexpected results were shown. Answer, page 11. However, as discussed below, the Examiner fails to provide any evidence as to why a *prima facie* case of obviousness was established. Therefore, the Examiner's allegation that the claims are obvious is without any support, other than an arbitrary, unsupported, and incorrect conclusion created entirely by the Examiner.

In presumably arguing that a *prima facie* case of obviousness was established, the Examiner alleges that: 1) a reasonable expectation of success was present because Prakash discloses low affinities of sulfone and sulfoxide metabolites to 5-HT2 and D2 receptors; and 2) metabolites of ziprasidone disclosed in Prakash are "indeed a salt form of ziprasidone," thus "the combined teachings of reference would have ... provided for methods of various forms of metabolites" of ziprasidone." Answer, pages 12-13. Appellants disagree.

First, even assuming that a reasonable expectation of success existed as the Examiner alleges, a *prima facie* case of obviousness still cannot be established in this case.[4] This is because other requirements for establishing a *prima facie* obviousness (*i.e.*, that the references must disclose all of the claim limitations and that a motivation to combine the references must exist, *see* Manual of Patent Examining Procedure, § 2143) are not met by the combination of references cited by the Examiner. As discussed above, the combination of references does not disclose the administration of any metabolite, much less a ziprasidone metabolite. Appellants previously submitted that those of ordinary skill in the art would not have been motivated to use ziprasidone metabolites because it was well-known in the art at the time of Appellants' invention that ziprasidone metabolites are generally inactive, and the activity of ziprasidone comes primarily from the parent drug. Brief on Appeal, pages 16-17. As evidence of this, Appellants submitted Ereshefsky, *J. Clin. Psychiatry*, 57 (suppl.11): 12-25 (1996) and Physician's Desk Reference, 56th Ed.,

[4] Appellants expressly dispute the Examiner's allegation that a reasonable expectation of successfully obtaining the claimed invention did exist. This is because Prakash, when considered as a whole, actually teaches away from the use of ziprasidone metabolites. *See* Brief on Appeal, pages 16-17.

page 2688 (2002). Without providing any evidence to the contrary, the Examiner simply concludes that a *prima facie* obviousness is established in this case based on a mere allegation that a reasonable expectation of success was present.

Second, as Appellants previously submitted, the Examiner's conclusion that metabolites of ziprasidone are a salt form of ziprasidone is legally and scientifically incorrect.[5] Brief on Appeal, pages 15-16. Disregarding evidence from a scientific dictionary that shows salts are not the same as metabolites, the Examiner alleges that Appellants' arguments are not "persuasive because the instant pending claims do not exclude the salts or metabolites described in the cited reference." Answer, page 12. However, Appellants point out that the pending claims do exclude the salts of ziprasidone itself, as disclosed in Lowe and Allen. Although some ziprasidone metabolites are disclosed in Prakash,[6] Lowe and Allen are irrelevant to the patentability of the pending claims, because salts of ziprasidone are not ziprasidone metabolites. Not only is the Examiner's allegation that "metabolites of Prakash are indeed a salt form of ziprasidone" scientifically incorrect, such a mere allegation, without providing further evidence to support it, cannot form a basis for rejecting the claims. *See In re Sang-Su Lee*, 277 F.3d at 1343-4.

For at least the foregoing reasons, Appellants submit that the rejection of claims 1-15 and 50-53 warrants reversal, and thus respectfully request the Board to overturn the rejection of these claims under 35 U.S.C. § 103.[7]

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[5] Appellants note that this allegation is not the only allegation that is scientifically incorrect. Appellants previously argued that ziprasidone itself should be inactive in order for the administration of a ziprasidone metabolite to result in the same *in vivo* activity as the administration of ziprasidone. Brief on Appeal, pages 17-18. The Examiner again mischaracterizes Appellants' argument to mean that ziprasidone itself should be inactive in order for the administration of a ziprasidone metabolite to result in any *in vivo* activity, and provides arguments irrelevant to Appellants' initial argument. *See Answer*, pages 13-14. The Examiner misses the point that the pharmacological effects obtained from the administration of a ziprasidone metabolite cannot be identical to that obtained from the administration of ziprasidone itself.

[6] For the reasons discussed in their Brief of Appeal, Appellants point out that no "administration" of a ziprasidone metabolite was disclosed in Prakash. In addition, Prakash teaches away from the claimed invention. *See* Brief on Appeal, pages 16-17.

[7] Appellants note that the patentability of claims 5, 50-51 and 52-53 are not separately disputed in the Answer. Appellants submit that for the reasons stated in their Brief on Appeal, these claims are further unobvious over the references cited by the Examiner.

C. *Zenith* is Irrelevant to the Patentability of the Pending Claims

In response to Appellants' argument that *Zenith Laboratories, Inc. v. Bristol-Myers Squibb Co.*, 30 U.S.P.Q.2d 1285 (Fed. Cir. 1994) is not relevant to the patentability of the pending claims, the Examiner maintains that it is applicable because "that which would literally infringe if later in time anticipates if earlier." Answer, pages 14-15, citing *Bristol-Myers Squibb Co. v. Ben Venue Lab, Inc.*, 246 F.3d 1368, 1378 (Fed. Cir. 2001). Again, the Examiner misses the point.[8]

Unlike the pending claims, those at issue in *Zenith* were directed to a compound, not a method of administering the compound. Therefore, even assuming the Examiner's interpretation of *Zenith* were correct, *Zenith* would still be irrelevant. Consequently, Appellants submit that the Examiner's reliance on *Zenith* is completely misplaced, and thus request that the Board overturn the rejection of the pending claims.

II. Conclusion

For the reasons stated above, in Appellants' Brief on Appeal, and in the record of this application as a whole, Appellants submit that the rejections of claims 1-15 and 50-53 are in error, and respectfully request the Board to overturn the rejections.

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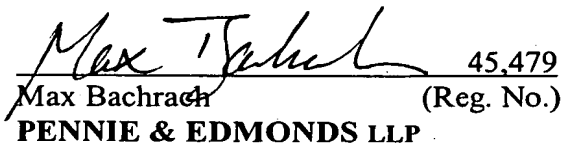
[8] *Bristol-Myers* held that the claims at issue were anticipated by a prior art reference because the performance of steps disclosed by the prior art reference would literally infringe the claims at issue. Therefore, the Court concluded that "it is axiomatic that that which would literally infringe if later anticipates if earlier." *Id.* Applying the same analysis in this case, Appellants point out that performing the steps disclosed in Davis (*i.e.*, administering ziprasidone to a patient) today would not literally infringe the pending claims (*i.e.*, claims to the administration of a ziprasidone metabolite). It follows, therefore, that Davis does not anticipate the pending claims.

No fee is believed due for the submission of this paper. However, if any fees are required for the submission of this paper or to avoid abandonment of this application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully Submitted,

Date: August 31, 2004



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